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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/535,951	03/27/2000	Alan D. Schreiber	555-56	4293

7590 06/25/2003

Nixon & Vanderhye PC
1100 North Glebe Rd 8th Floor
Arlington, VA 22201-4714

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/25/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/535,951	SCHREIBER, ALAN D.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendments filed April 18, 2003 have been entered.

The addition of claims 14-17 in amendments filed April 18, 2003 is acknowledged.

The outstanding rejection under 35 USC 112, second paragraph with regard to claims 10-12 is withdrawn in view of the amendments.

The outstanding rejection under 35 USC 103

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for progestational agents recited in claims 9 and 14-17, does not reasonably provide enablement for other progestational agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide sufficient information to enable one of skilled in the art to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue

experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The instant claim is very broad. It encompasses all progestational compounds that have an effect on the function of the sex organs of said mammal less than that of the equivalent dose of medroxyprogesterone. Applicant fails to set forth the criteria that defines what "function of the sex organs" would be effected by the progestational agents. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "progestational agents that have an effect on the function of the sex organs of said mammal less than that of the equivalent dose of medroxyprogesterone" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "

progestational agents that have an effect on the function of the sex organs of said mammal less than that of the equivalent dose of medroxyprogesterone ", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Although the applicant points out the various binding affinity of different progestational compounds through the teachings of Terenius (reference provided by the applicant), Terenius does not correlate the binding affinity to the functions on the sex organs for those compounds. It is well-known that binding affinity is an indication of selectivity, not the potency. It is apparent that the instant claim encompasses all progestational compounds that less potent than medroxyprogesterone. However, it is unclearwhat progestational compounds or how to select them based on the instant disclosure. Applicant uses functional language in attempt to define the instant invention. Attention is directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a functional claim exists not only when a claims is "wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty". Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outlin[e] goals appellants hope the recited invention achieves and

the problems the invention will hopefully ameliorate". Applicants functional language at the point of novelty fails to meet the requirements set forth under 35 USC 112, first paragraph. Claims employing functional language at the point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limits of the monopoly asserted" *General Electric Company v. Wabash Appliance Corporation et* supra, at 468. Claims thus constructed provide no guidance as to medicaments employed, levels for providing therapeutic benefit, or provide notice for those practicing in the art, limits of protection. Simply stated, the presented claims are an invitation to experiment, not reciting a specific medicament regimen useful for practicing the instant invention. Recently, the court, in the case *University of Rochester v. G.D. Searle & Co. Inc.* 249F. Supp.2d 216,(W.D. N.Y. 2003), with regard to using merely functional language to describe an invention, further rules that in order "to practice the invention claimed in the patent, a person of ordinary skill in the art could have to engage in undue experimentation, with no assurance of success." Such functional limitations essentially call for the use of trial and error to attempt to find a compound that will perform the herein claimed function in the instant application. "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the germ of an idea does not constitute enabling disclosure." *Genetech*, 108 F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful

conclusion")). Therefore, absent sufficient and reasonable detail provided by the applicant, the instant claims fail to comply with the enablement requirement set forth in. 35 USC 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "progestational agent that has an effect on the function of the sex organs of said mammal **less than** that of an equivalent dose of medroxyprogesterone" in claim 8, line 4 renders the claims indefinite. It is unclear what progestational agents are encompassed by the claim. Further, the nature of "function" on the sex organs encompassed by the claims is unclear. Without knowing exactly what effects and the degree on the function of the sex organs may encompassed by the claim, one of ordinary skill in the art would not know what progestational agents are considered to be encompassed by the claims as being lesser in such effect than medroxyprogesterone.

Response to the arguments

Applicant's rebuttal arguments filed April 18, 2003 averring the effects of progestational agents on uterus can be measured by the affinity of the binding of the agents to the rabbit uterus have been considered, but are not found persuasive. As

discussed above, binding affinity is an indication of selectivity, not the potency. Therefore, it would not know what agents are encompassed by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cincotta (US Patent 5,565,454) in view of de Gruijter et al. (Metabolism, 1991; 40(11):1119-1121), reference of record.

Cincotta et al. teaches a method of in treating atherosclerosis using prolactin enhancer and/or prolactin inhibitors including haloperidol (see particular Col. 1, line 32 - Col.2, line 15; also Col.2, line 25 – 34; also Col.6, line 5-9). Cincotta et al. also teaches that prolactin enhancer could reduce the plasma triglyceride and cholesterol level (See col. 2, line 25-36). Cincotta et al. teaches that platelets and monocytes adhesion to the endothelium connective tissues may lead to restenosis (See col. 1, line 48 - col.2, line 15).

Cincotta et al. does not expressly teach the use of haloperidol specifically in a method of reducing atherosclerotic plaque.

de Gruijter et al. teaches Hypercholesterolemia or combined Hypercholesterolemia-hypertriglyceridemia increase the adhesion of monocytes to the

endothelium of the vessel wall that result in atherosclerotic plaque (See abstract and page 1121, col. 1).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to use haloperidol in a method to reduce atherosclerotic plaque.

One of ordinary skill in the art would have been motivated to use haloperidol in a method to reduce atherosclerotic plaque because any known prolactin modulator compounds, including haloperidol, would have been reasonably expected to be useful in a method of reducing the platelets and monocytes adhesion to the endothelium or subendothelial connective tissue and reducing the plasma cholesterol and triglyceride level in patients. Elevated cholesterol and triglyceride level and increased adhesion of moncytes to the endothelium of bloods vessel walls are known to increase the formation of atherosclerotic plaque. Therefore, reducing the plasma triglyceride and cholesterol level and adhesion of platelets and moncytes to the endothelium of blood vessel walls by a known prolactin enhancer such as haloperidol would have been reasonably expected to reduce atherosclerotic plaque based on the cited prior art, absent evidence to the contrary.

Response to Arguments

Applicant's arguments filed April 18, 2003 averring the cited prior art's failure to teach *in vivo* study have been fully considered but they are not persuasive. de Gruijter et al. assess the adhesion capacity of human monocytes from different groups of patients and found that moncytes from patients with Hypercholesterolemia or combined Hypercholesterolemia-hypertriglyceridemia are more adherent to HUVEC. The

reasonable expectation is present because the study is based on the *in vivo* observation in animal model that hypersholesterolemic animals have increased adhesion of moncytes to the endothelium, which leads to the development of atherosclerotic plaque.

New ground of rejection

Claims 8-9, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garfield (WO 96/09826).

Garfield teaches a method of treating atherosclerosis employing progesterone compounds (See page 1, line 7-8; also claim 1). Garfield also teaches that suitable progestin employed as hydroxyprogesterone, progesterone, and northindrone (See claims 1 and 10). Garfield also teaches that progestin act synergistically with prostacyclin in the endogenous platelet inhibitory and antithrombogenic activities (See page 3, lines 1-31; also page 10, lines 25-30). Garfield also teaches the regimen of progestin, estrogen, and prostacyclin is useful in reducing aortic atheromatous plaques and treating preeclampsia, which is considered as an acute form of atherosclerosis (See page 4, lines 4-5; also page 5, line 8-23).

Garfield does not expressly teach the method of administering progestin as useful to reduce atherosclerotic plaque load.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method of Garfield to reduce atherosclerotic plaque load.

One of ordinary skill in the art would have been motivated to employ the method of Garfield to reduce atherosclerotic plaque load since the regimen of Garfield is known to reduce aortic atheromatous plaques through reducing the platelet aggregation. Administering progestin, along with estrogen and prostacyclin would be reasonably expected to be beneficial in reducing atherosclerotic plaque.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coughlin (US Patent 4,444,778).

Coughlin teaches that serotonin receptor blockers, broadly, are useful in treating atherosclerosis (See the abstract and col. 5, lines 60-65). Coughlin teaches serotonin receptor blockers including butyrophenones such as haloperidol are effectively blocking the smooth muscle cell proliferation, which is lead to atherosclerotic conditions (See col. 4, lines 40-43; also col. 3, line 44-57).

Coughlin does not expressly teach the use of haloperidol or butyrophenones to reduce the atherosclerotic plaque load.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ butyrophenones such as haloperidol specifically in a method to reduce atherosclerotic plaque load.

One of ordinary skill in the art would have been motivated to employ butyrophenones such as haloperidol in a method to reduce atherosclerotic plaque load. It is known that serotonin receptor blockers as useful in treating atherosclerosis. Therefore, employing any known serotonin receptor blockers including haloperidol, an

agent specifically taught to be similar to the preferred agent, pizotyline, would be reasonably expected to be useful in treating atherosclerosis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617
June 24, 2003